Nonlinear Dynamics of Heart Rate Variability in Children with Asthmatic Symptoms

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Abstract— **Asthma is a chronic lung disease that is prone to start during chilhood. Although symptoms can be usually controlled with medication, early diagnosis is crucial to reduce the risk of permanent airway obstruction. Despite the fact that origin of asthma is still uncertain, abnormal parasympathetic nervous system (PNS) activity has been pointed out to play a major role in its pathogenesis. In this work the use of nonlinear heart rate variability (HRV) indexes is proposed in order to look for differences between children classified as high- or low-risk of suffering from asthma in the future. PNS activity is assessed trough a filtered HRV signal. Correlation dimension analysis showed statistically significant differences distinguishing high- and low-risk. Decreased complexity observed in high-risk group suggests that abnormal PNS activity might be related with increased risk of developing asthma.**

Keywords— **heart rate variability, asthma, children, nonlinear, parasympathetic nervous system**

I. Introduction

Asthma is a chronic lung disease that inflames and narrows the airways [1], and although it affects people of any age [2] it most often starts during childhood [3]. Despite the fact that main symptoms of asthma (increase in mucus segregation, spasmodic contraction of the bronchioles or bronchial hyper-responsiveness) are usually reversible with medication, their effect can become severe in some cases [2]. Therefore, early diagnosis of asthma is crucial to prevent patients from the worsening of these symptoms, that could turn into permanent airway obstruction [4].

Although diagnosis of asthma is well defined in adults, the assessment in young children is performed through evaluation of the clinical history [5] that can be incomplete or inaccurate in some cases.

Abnormal parasympathetic nervous system (PNS) activity has been related with the pathogenesis of asthma [6], playing a major role in the bronchoconstriction mechanisms [7] and in the control of bronchomotor tone [8]. Heart rate variability (HRV) analysis can be used for assessing PNS activity and nonlinear dynamics analysis is considered to be a powerful tool in the evaluation of cardiovascular system behavior [9]. In this way, a nonlinear analysis of HRV is proposed here in order to assess differences in the complexity of PNS activity as an indicator of increased risk of developing asthma.

II. Materials

The data base analyzed in this work is composed by 34 children who were referred to the Pediatric Allergy Unit of Helsinki University Hospital due to persistent or recurrent lower respiratory tract symptoms. From each patient, long-term electrocardiogram (ECG) holter recording was acquired. The recording devices as well as the acquisition method itself were custom designed at Tampere University of Technology (Tampere, Finland) [10]. The sampling frequency of the ECG recordings was 256 Hz, and the patients were classified in different groups according to their modified asthma predictive index (mAPI) [11]. A high risk (HiR) group for developing asthma was formed by 13 children with positive mAPI, while a low risk (LoR) group was composed by 14 children with negative mAPI. A third group was formed with 7 children with a confirmed history of wheeze but that were under inhaled corticosteroids (ICS) treatment at the time of the recording. Additional information about this data can be found from *Seppä et al.* [10].

Data acquisition was approved by an institutional pediatric ethics review board and informed written consent was received from guardians of all patients. Also informed written parental consent was received before data acquisition.

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III. METHODS

A. Preprocessing

ECG signals were only analyzed during night. In the first place, recordings were not performed under a controlled environment, so daily activity of the children was unknown. Furthermore, both cardiac vagal tone and parasympathetic effect over bronchomotor tone appear to be increased during night [12], so night time is regarded as an interesting analysis period. Thus, a reduction in mean heart rate (HR) was observed between 23:00 p.m. and 05:00 a.m., so analysis period was set to this interval as patients can be considered to be at a resting/sleeping state. The preprocessing of the signals was structured in different steps:

- Interpolation of the ECG signals to 1000 Hz using cubic splines in order not to compromise HRV analysis.
- Detection of QRS complexes using a wavelet-based detector [13].
- Ectopic beat detection and correction based on instantaneous HR variation. Afterwards, RR interval series were generated and interpolated to 4 Hz.
- Signal quality evaluation: signal to noise ratio (SNR) was beat-to-beat calculated over the ECG signals. Those beats for which a SNR threshold (set as half the median SNR of the night period of the recording) was not exceeded were labeled as low-quality and not considered in the analysis.
- RR series were split in overlapped five-minute blocks (number of samples is enough for nonlinear analysis) with four-minute overlap for the subsequent analysis.

As we are mainly interested in PNS activity, two filtered versions of the RR interval series were also obtained with two different approaches, so that the influence of both sympathetic activity and high frequencies with uncertain origin is reduced. In the first approach (approach A), we obtained a new series, $\widetilde{\mathrm{RR}}^{\mathrm{A}}$, by filtering the RR series with a 10^{th} order band-pass Butterworth filter with 0.15 and $\overline{\mathrm{HR}}/2$ cut-off frequencies (being $\overline{\mathrm{HR}}$ the mean HR of the analyzed segment). Hence, only high frequency (HF) components are preserved.

In the second approach (approach B), we proposed to use a filter that only preserves those frequency components close to the maximum peak of the power spectral distribution (PSD) in the band [0.15-$\overline{\mathrm{HR}}/2$] Hz, which is considered to be related with respiration. The new series was named $\widetilde{\mathrm{RR}}^{\mathrm{B}}$. The filter ($10^{th}$ order Butterworth band-pass filter with a 0.15 Hz bandwith) was recalculated for each segment so that it is centered in the frequency corresponding to that maximum (F_m). An example of this filtering is displayed in Fig. 1.

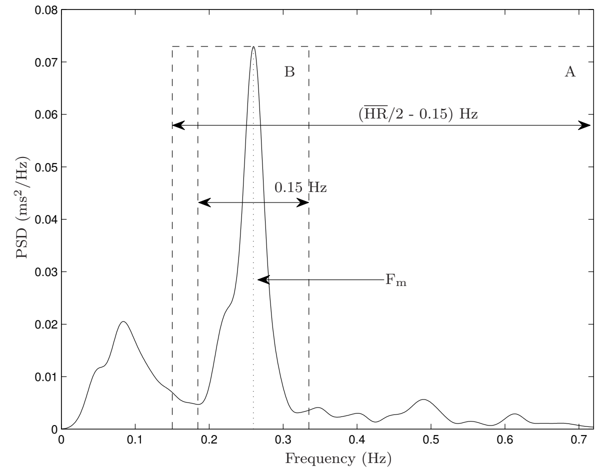

Fig. 1: PSD of a five-minute segment of the RR interval series. The frequency components preserved after filtering are shown for both approaches (dashed-lines). Note that in the case of approach B (0.15 Hz bandwith), the filtering window is centered in the frequency corresponding to the maximum ($\mathrm{F_m}$, dotted line) in the band [0.15-$\overline{\mathrm{HR}}/2$] Hz.

B. Nonlinear indexes

In this work, three nonlinear HRV indexes were considered in the analysis:

- **Correlation dimension** ($\mathrm{D_2}$): it constitutes a measurement of the complexity of a system.
- **Approximate entropy** ($ApEn$): it is a measure of time series regularity, and it can be used to describe the unpredictability degree of a finite length signal.
- **Sample entropy** ($SampEn$): it is based on $ApEn$, and it is considered more robust in short data sections.

The calculation of the three indexes is performed as in [14] (in the case of $\mathrm{D_2}$, it is calculated as $\widehat{\mathrm{D}}_{2(\mathrm{max})}$ [14]). Concerning the parameter selection, all the presented indexes are dependent on the embedding dimension, m, and the threshold, r. $\mathrm{D_2}$ was computed by varying m from 1 to 16 and r from 0.01 to 3 in 0.01 steps in order to maximize correlation dimension. For $SampEn$, $m = 2$ and $r = 0.15$ were used, while for $ApEn$ $m = 2$, and the value of r was selected for maximizing the approximate entropy ($ApEn_{max}$).

These three indexes can be regarded as measurements of the complexity of the underlying mechanisms. In our study we applied them to the RR, $\widetilde{\mathrm{RR}}^{\mathrm{A}}$ and $\widetilde{\mathrm{RR}}^{\mathrm{B}}$ series. The indexes obtained from $\widetilde{\mathrm{RR}}^{\mathrm{A}}$ are referred to as $\widetilde{\mathrm{D}}_2^{\mathrm{A}}$, $\widetilde{ApEn}_{max}^{\mathrm{A}}$ and $\widetilde{SampEn}^{\mathrm{A}}$, while in the case of $\widetilde{\mathrm{RR}}^{\mathrm{B}}$, the indexes are referred to as $\widetilde{\mathrm{D}}_2^{\mathrm{B}}$, $\widetilde{ApEn}_{max}^{\mathrm{B}}$ and $\widetilde{SampEn}^{\mathrm{B}}$.

Patient characterization was accomplished by the median of the minute by minute evolution of each of the calculated indexes along the whole analysis period. In this way, e.g., D_2 was calculated as $median([D_2^1,...,D_2^i,...,D_2^N])$, being D_2^i the correlation dimension obtained from the i^{th} five-minute segment of the RR series, whereas $\widetilde{D}_2^A$ was calculated as $median([\widetilde{D}_2^{A,1},...,\widetilde{D}_2^{A,i},...,\widetilde{D}_2^{A,N}])$, being $\widetilde{D}_2^{A,i}$ the correlation dimension of the i^{th} five-minute segment of the $\widetilde{RR}^A$ series.

For comparison purposes, mean normal-to-normal (NN) interval ($\overline{NN}$), standard deviation of NN interval (SDNN), low frequency power (P_{LF}), high frequency power (P_{HF}), P_{LF} to P_{HF} ratio (P_{LF}/P_{HF}) and normalized P_{HF} (P_{HFn}) were calculated from the original interpolated RR interval series.

C. Statistical methods

For the three study groups, a Kolmogorov-Smirnov test was applied to assess normality of the data. Afterwards, a two-sided Wilcoxon rank-sum test was applied when needed, in order to check if any difference between pairs of groups can be found. Bonferroni correction was applied for Wilcoxon test, thus leading to consider $p < 0.017$ (as there are three groups, $p = 0.05/3$).

Table 1: Median (IQR) of the presented indexes for each group. Significant differences are labeled with * when comparing HiR and LoR and with # when comparing ICS and LoR.

	LoR (n=14)	HiR (n=13)	ICS (n=7)
$\overline{NN}(ms)$	769.9 (137.3)	777.0 (170.9)	790.1 (80.1)
$SDNN(ms)$	66.7 (22.5)	59.7 (93.2)	101.7 (38.2)
$P_{LF}(ms^2)$	1189 (817)	1112 (1713)	1756 (1247)
$P_{HF}(ms^2)$	1592 (669)	1213 (5649)	3927 (2906)
P_{LF}/P_{HF}	0.67 (0.37)	0.48 (0.29)	0.42 (0.09)#
P_{HFn}	0.60 (0.13)	0.68 (0.12)	0.70 (0.05)#
D_2	3.79 (0.10)	3.68 (0.18)	3.56 (0.10)
$\widetilde{D}_2^A$	3.57 (0.31)	2.43 (0.37)	3.37 (0.28)
$\widetilde{D}_2^B$	2.68 (0.37)	2.44 (0.24)*	2.45 (0.28)
$ApEn_{max}$	0.91 (0.03)	0.91 (0.06)	0.88 (0.06)
$\widetilde{ApEn}_{max}^A$	0.70 (0.08)	0.68 (0.06)	0.64 (0.03)
$\widetilde{ApEn}_{max}^B$	0.56 (0.02)	0.56 (0.02)	0.56 (0.03)
$SampEn$	0.36 (0.19)	0.38 (0.12)	0.43 (0.08)
$\widetilde{SampEn}^A$	0.43 (0.10)	0.46 (0.07)	0.48 (0.04)
$\widetilde{SampEn}^B$	0.49 (0.04)	0.47 (0.03)	0.49 (0.02)

IV. RESULTS

The medians of each of the analyzed indexes for each group are displayed in Table 1. From these results it can be noticed that $\widetilde{D}_2^B$ is the only parameter that is able to distinguish between LoR and HiR groups. However, a tendency towards different median values between both groups is observed for P_{LF}/P_{HF} and P_{HFn}. Also D_2, $\widetilde{D}_2^A$, $\widetilde{D}_2^B$ and $\widetilde{ApEn}_{max}^A$ show tendencies toward different medians in LoR and ICS.

Looking at Table 1, the values obtained for D_2 and $ApEn_{max}$ decrease as the filtering becomes more restrictive. However, in the case of $SampEn$ the behavior is the opposite. It can be noticed that filtering processes slightly enhance the differences existing in median D_2 between LoR and HiR, although this comes together with an increase of the IQR in the case of $\widetilde{D}_2^A$ and $\widetilde{D}_2^B$. Regarding at $ApEn_{max}$ and $SampEn$, the distinct filtering do not modify the difference between medians of LoR and HiR significantly, but the IQR is reduced in general, thus making the measurements more stable.

V. DISCUSSION

The important role of PNS in bronchomotor tone control [8] and its implication in bronchoconstriction mechanisms [7] have led to suggest a relationship between abnormal PNS activity and pathogenesis of asthma [6]. Analysis results were only obtained over those segments with assumed good signal quality, being the mean SNR of the recordings 43.55 dB. Lack of significant differences between groups for $\overline{NN}$, SDNN, P_{LF}, P_{HF}, P_{LF}/P_{HF} and P_{HFn} might be explained by high inter-subject variability represented by the high IQR values observed in Table 1. This effect is specially relevant in P_{HF}, showing a lower median value for HiR than for LoR, whereas higher values would be expected. The extremely high IQR could explain the absence of significance for this index. Tendency towards higher P_{LF}/P_{HF} and P_{HFn} in HiR might reflect parasympathetic dominance. These indexes are able to distinguish between LoR and ICS, although the reduced number of patients in ICS compromises the further physiological interpretation.

On the other hand, nonlinear analysis of HRV has been reported to be able to quantify the complexity of ANS activity [9, 14]. In this way, nonlinear analysis based on the calculation of D_2, $ApEn_{max}$ and $SampEn$ was performed. The effect of the different sleep stages over HRV analysis [15] was taken into account here by obtaining the median of the whole night period, thus minimizing their influence. The results of this approach (Table 1) showed no differences between groups. However, a tendency towards lower D_2, i.e., lower overall complexity, can be noticed in ICS with respect to the other groups. Again, interpretation is compromised in ICS.

Two different approaches were proposed in order to analyze only those components with parasympathetic activity dominance. In approach A, a band-pass filtering that rejects those frequency components outside the HF band (0.15-$\overline{\mathrm{HR}}/2$ Hz) was employed. Nonlinear analysis performed over the resulting series, $\widetilde{\mathrm{RR}}^{\mathrm{A}}$, was not able to differentiate any pair of groups, although a tendency towards lower $\widetilde{ApEn}_{max}^{\mathrm{A}}$ was observed in ICS with respect to the other groups.

In this way, approach B is based on a filtering procedure whose aim is to keep only the information that is related to this respiratory modulation. The results obtained for $\widetilde{\mathrm{D}}_2^{\mathrm{B}}$ showed reduced complexity in HiR with respect to LoR, what might indicate a reduction in the number of degrees of freedom in the case of HiR, i.e., a reduction in the adaptability of PNS. The fact that significant results were only obtained from the $\widetilde{\mathrm{RR}}^{\mathrm{B}}$ series reveals that differences between patients are enhanced by the respiration-related PNS activity.

On the other hand, $ApEn_{max}$ and $SampEn$ were not able to distinguish between any pair of groups either when calculated from the filtered or the non filtered RR interval series. This may reveal that some of the features of the signals remain hidden in a low-dimensional analysis (in the case of $\widetilde{\mathrm{D}}_2^{\mathrm{B}}$, m is varied from 1 to 16). Also, in Table 1 the median of D_2 and $ApEn_{max}$ are reduced after the filtering, as removing non-redundant information goes along with a complexity and irregularity reduction, respectively. On the contrary, median $\widetilde{SampEn}^{\mathrm{A}}$ and $\widetilde{SampEn}^{\mathrm{B}}$ are larger than median $SampEn$ (although not showed here, same tendency was assessed for $ApEn$). This unusual behavior corresponds to the effect of the threshold r parameter selection, which was 0.15 for all $SampEn$ estimates instead of being adjusted as for $ApEn_{max}$.

Even though a reduction in the complexity of biological systems is usually related with illness [9, 14], the physiological underlying mechanisms leading to it are often difficult to interpret. In our case, the decreased complexity reported in HiR patients could be related either to a reduction of PNS adaptability or with an increase of the respiratory system stability, which might be reflected in HRV analysis. Nonetheless, both hypotheses point out to abnormal PNS activity to be associated with risk of developing of asthma.

VI. Conclusion

A characterization of different children classified as high- or low-risk of suffering from asthma through nonlinear HRV analysis has been performed here. The results show that decreased complexity of PNS activity is observed in the HiR group, thus corroborating that altered PNS behavior is closely related to increased asthma risk. As abnormal PNS activity is measurable trough nonlinear HRV analysis, it could constitute an interesting tool for complementing the current methods to evaluate asthma risk in preschool children.

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